

# Rib Hypoplasia and Double Aortic Arch in an Infant with Thrombocytopenia Absent Radius Syndrome

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## ABSTRACT

Thrombocytopenia-absent radius (TAR) syndrome is characterized by the absence of a bone called the radius in each forearm and a shortage (deficiency) of blood cells involved in clotting (platelets). Thrombocytopenia prevents normal blood clotting, resulting in easy bruising and frequent nosebleeds. Potentially life-threatening episodes of severe bleeding (hemorrhages) may occur in the brain and other organs, especially during the first year of life. Hemorrhages can damage the brain and lead to intellectual disability. Affected children who survive this period and do not have damaging hemorrhages in the brain usually have a normal life expectancy and normal intellectual development. This platelet deficiency (thrombocytopenia) usually appears during infancy and becomes less severe over time; in some cases the platelet levels become normal. We present a case of a term male diagnosed postnatally with Thrombocytopenia Absent Radius (TAR) syndrome with right-side dominant double aortic arch, absent right fourth rib and extreme hypoplasia of his left fourth and fifth ribs. These anomalies suggest possible new phenotypic features of TAR syndrome.

**Keywords:** Birth defects; Dysmorphology; Collagen; Vascular; Multisystem disorders

## INTRODUCTION

Thrombocytopenia Absent Radius (TAR) syndrome, (MIM 274000) typically presents with bilateral absent radius with both thumbs present and thrombocytopenia. It can involve other skeletal anomalies as well as potentially affect the heart and/or genitourinary system. The diagnostic criteria include: 1) bilateral absence of the radius in the presence of both thumbs and 2) thrombocytopenia, usually  $<50,000/\text{mCL}$  [1]. Lower limb anomalies are present in more than half of affected individuals and usually are less severe than upper limb anomalies. Thrombocytopenia, which is usually transient, is seen in all cases and is usually symptomatic for the first few months of life but can last until school age. TAR syndrome typically affects fewer than 1 in 100,000 newborns. The inheritance pattern is autosomal recessive, typically associated with biallelic mutations of the RNA-binding motif protein 8A gene, RBM8A, located in trans on chromosome 1q21.1. We present a case of a term male diagnosed postnatally with TAR syndrome with the incidental finding of cardiovascular structural disease of a vascular ring, absent right fourth rib, and extreme hypoplasia of his

left fourth and fifth ribs.

## CASE STUDY

The male infant was born at 39 weeks 2 days via vaginal delivery to a primigravid 31-year-old mother. Apgar scores were 8 and 9 at 1 and 5 minutes, birth weight was 2570 g (5.66th percentile), length was 47.2 cm (14.87th percentile), and head circumference was 31 cm (2.05th percentile). Prenatally, at the 20-week gestation anatomical survey, he was found to have bilateral flexed hands, bilateral absent radius, possible atrial aneurysm with a possible right aortic arch, and suspected vascular ring. Initial physical examination of the neonate revealed chest wall asymmetry with no palpable left anterior 4th and 5th ribs, a visible precordial pulse through the chest defect, and shortened upper extremities with bilateral radial club hand and thumbs present bilaterally. No right-sided rib anomalies were noticed upon physical exam.

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Initial laboratory testing revealed severe thrombocytopenia—platelet count of 11,000/mcL at approximately 12 hours of life—and an elevated white blood cell count of 46,500/mcL with no other abnormalities. Radiographs of his upper extremities and chest confirmed bilateral absent radius, absent right fourth rib, and hypoplasia of the left 4th and 5th ribs (Figure 1). An echocardiogram showed a right aortic arch with an aberrant left subclavian artery concerning for a vascular ring. Computerized tomography angiography (CTA) of his chest identified a double aortic arch with a dominant right arch and tracheal compression, all suggestive of a vascular ring (Figure 2). The CTA allowed for three-dimensional reconstruction of his skeleton that clearly revealed absent right fourth and hypoplastic left 4th and 5th ribs. Given his absent radii, presence of thumbs, and severe thrombocytopenia, he was suspected of having TAR syndrome. During his hospitalization, the patient continued to have severe thrombocytopenia (18,000), requiring several platelet transfusions.



**Figure 1:** Chest X-Ray demonstrating rib anomalies. Arrows pointing to absent right fourth rib and hypoplasia of left fourth and fifth rib.



**Figure 1:** CTA demonstrative aortic vascular ring. RA for right arch and LA for left arch.

RBM8A sequence analysis and CNV analysis revealed compound heterozygous pathogenic variants: a c.-21G>A transition in the 5' untranslated region and a c.487C>T transition in exon 6

(p.Arg163Term). Both changes have been previously reported individually in patients with TAR syndrome. SNP microarray (Affymetrix CytoScan HD microarray) and sequence and CNV analyses of TBX5 were normal. Chromosome breakage analysis was not done.

## RESULTS AND DISCUSSION

The primary features of this infant's radial anomalies are shared by several syndromes, most notably Fanconi Anemia (FA), TAR syndrome, and Holt-Oram syndrome (HOS) [1-3]. FA, however, is characterized by pancytopenia, absent, hypoplastic, or malformed thumbs, short stature, and frequently other malformations, TAR syndrome by bilateral absent radius, the presence of both thumbs, and thrombocytopenia [1] and HOS by absent, hypoplastic, or triphalangeal thumbs, upper extremity defects, cardiac malformations (usually septal defects), and no hematologic abnormality [3]. The congenital thrombocytopenia and presence of both thumbs in our patient were most suggestive of TAR syndrome. Additionally, infants with TAR syndrome can present with a leukemoid reaction [1] which was evident in this case with an elevated WBC that decreased to normal values for age within 24 hours. Although other cardiac and thoracic skeletal anomalies may occur in the TAR syndrome, absent or hypoplastic thoracic ribs and double aortic arch have not been reported previously. Both of this infant's mutations are among those that are most commonly characterized in patients with TAR syndrome. After extensive literature and gene database search, the primary phenotype associated with a c.-21G>A transition in the 5' untranslated region of the RBM8A gene is TAR syndrome; however, it has been found in some patients with Müllerian duct malformations in Mayer-Rokitansky-Küster-Hauser syndrome [4-6].

## CONCLUSION

The c.487C>T transition in exon 6 (p.Arg163Term) is thus far only seen in TAR. This case expands the phenotype of the TAR syndrome to include vascular ring and absent/hypoplastic ribs. To our knowledge, this is the first case of TAR syndrome with this constellation of findings.

The severity of skeletal problems in TAR syndrome varies among affected individuals. The radius, which is the bone on the thumb side of the forearm, is almost always missing in both arms. The other bone in the forearm, which is called the ulna, is sometimes underdeveloped or absent in one or both arms. TAR syndrome is unusual among similar malformations in that affected individuals have thumbs, while people with other conditions involving an absent radius typically do not. However, there may be other abnormalities of the hands, such as webbed or fused fingers (syndactyly) or curved pinky fingers (fifth finger clinodactyly). Some people with TAR syndrome also have skeletal abnormalities affecting the upper arms, legs, or hip sockets.

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